Clinical Commentary Review

Idiopathic Anaphylaxis

Paul A. Greenberger, MD[a], and Phillip Lieberman, MD[b] *Chicago, Ill; and Memphis, Tenn*

Idiopathic anaphylaxis is a perplexing problem that accounts for approximately 30% to 60% of cases of anaphylaxis in ambulatory adults and perhaps 10% of cases in children. Advances in our knowledge of idiopathic anaphylaxis have occurred over the past decade with the elucidation of mast cell activating disorders and the discovery of episodes of anaphylaxis caused by galactose-alpha-1,3-galactose. Most patients do well because fatalities can usually be prevented with proper therapy, and many individuals, for reasons not understood, undergo spontaneous remission. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)

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The first report of patients with multiple episodes of anaphylaxis without discernible cause was published in 1978.[1] The investigation originated at the Northwestern University Medical School, Division of Allergy-Immunology, under the direction of the late Roy Patterson, MD. Many of the subsequent reports that deal with this disorder have come from the same institution. Since the original article, there have been a total of 102 published articles that deal directly with this condition or that indirectly clarify its diagnosis, natural history, and treatment.[2-92] The diagnosis of idiopathic anaphylaxis is one of exclusion. Patients with idiopathic anaphylaxis also may have experienced anaphylaxis from recognizable causes such as foods (5%)[17] or exercise (11%).[17] Pre-existing urticaria and/or angioedema had occurred in 23% of the Northwestern series of 335 patients with idiopathic anaphylaxis, and, during episodes, all the patients had either urticaria, angioedema, or both.[17] The typical attack began suddenly and reached a peak over minutes to a few hours. But a few patients reported urticaria for 3 days before anaphylaxis occurred.[7] Furthermore, from the series of 335 patients, 15 patients (4.5%) had known reactivity to nonselective nonsteroidal anti-inflammatory agents, and 65 (19%) reported penicillin allergy.[17] But, episodes of idiopathic anaphylaxis were distinct and not explained by such exposures or alternative diagnoses.[7] These findings imply that the physician may need to reassess the working diagnosis of idiopathic anaphylaxis.

It was noted early on that the manifestations of idiopathic anaphylaxis are identical to those that occur during episodes with known cause.[4-6] As more patients were reported, other key features were discovered. Many patients had severe life-threatening events,[9,10] and fatalities occurred.[18] Patients with idiopathic anaphylaxis were found to have a high incidence of atopy, as high as 58% in 1 series,[32] and there was a significantly higher incidence in women, than in men,[26,32] after puberty and until menarche at which time the incidence became equal. For many years, reports of idiopathic anaphylaxis were limited to the United States. However, beginning in the 1990s, reports began to appear from other countries, including Spain,[29] France,[31,32] Ireland,[33] Germany,[34] and Brazil.[35]

INCIDENCE

The exact incidence of idiopathic anaphylaxis is unknown. In 1995, Patterson et al[16] estimated the incidence in the United States (population 263,000,000) to be between 20,592 and 47,024 cases based on a survey of allergists and extrapolation to 4000 allergists in the United States. At that time, the current total number of identified cases of idiopathic anaphylaxis by allergists in the United States was 1020. Thus, it was assumed that the majority of cases went unreported.

An insight into the incidence can be obtained by ascertaining the percentage of cases of patients who presented with anaphylaxis to an allergist-immunologist and remain idiopathic after an extensive evaluation to determine the cause. In a population skewed to adults, approximately one-third[11] to two-thirds[26] of episodes have no known cause. It should be noted that in the study that shows a two-thirds incidence, episodes due to allergen immunotherapy and insect stings were excluded.[26] This exclusion would tend to produce a higher incidence than if these causes were included in the series. In children, the incidence of idiopathic anaphylaxis is much lower, but episodes in children have been reported.[21,22,45] Regardless of the overall incidence, in any given patient, idiopathic anaphylaxis can have a profound effect on quality of life because there is no known way for a patient to avoid a potential trigger.

THEORIES OF PATHOGENESIS

Serum tryptase is elevated acutely but is usually normal, <11.4 ng/mL, at baseline. Similarly, urine histamine or its

[a]Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Ill
[b]Divisions of Allergy and Immunology, Departments of Medicine and Pediatrics, University of Tennessee, Memphis, Tenn

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Corresponding author: Phillip Lieberman, MD, Divisions of Allergy and Immunology, Departments of Medicine and Pediatrics, University of Tennessee, 7205 Wolf River Blvd, Suite 200, Memphis, TN 38138. E-mail: aac@allergymemphis.com.

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TABLE I. Theories offered to explain episodes of idiopathic anaphylaxis

Hidden allergen
Aberrant cytokine profile lowering the threshold for mast cell degranulation
Female hormone effect on mast cells and/or basophils
An alteration in the T-cell population
Increased sensitivity to histamine at the target organ site
Presence of serum histamine releasing factor
Presence of IgE autoantibodies

metabolite can be elevated acutely. Several attempts have been made to discern the underlying cause of mast cell activation. Theories that resulted from these attempts are summarized in Table I. Perhaps the earliest hypothesis as to the origin of idiopathic anaphylaxis was the postulation that episodes were really antigen and/or allergen related, with failure to detect the culprit. Such a "hidden allergen" might exist as a food additive because there was no test to detect the presence of specific IgE to such ingredients. Investigators pursued this hypothesis by performing oral challenge tests with food additives in a blinded manner. They found that food additives, for example, potassium metabisulfite, failed to trigger episodes with patients in whom they were suspected to be responsible.[56] In addition, studies carried out to identify reproducible reactions to monosodium glutamate[87] and aspartame[88] could not confirm reactions even if people were emphatic about the connection. Alternatively, 2 health care workers were referred with a provisional diagnosis of idiopathic anaphylaxis and were found to have latex allergy such that avoidance of latex was associated with no additional episodes of anaphylaxis.[93]

Extensive food testing has been shown to uncover the culprit in some cases of anaphylaxis previously diagnosed as or suspected to be idiopathic.[37] In a study of 102 patients initially diagnosed as having experienced episodes of idiopathic anaphylaxis, a battery of 79 food-antigen skin prick tests were selected to include foods reported or suspected of provoking episodes. Previously, a detailed history, results of a physical examination, and results of conventional laboratory tests had ruled out all known causes of anaphylaxis. Thirty-two patients (31%) had positive tests to one or more food antigens. With 5 of these patients, subsequently eating a food that elicited a positive test provoked an anaphylactic event. Two patients who eliminated the foods completely stopped having reactions. The researchers concluded that a battery of selective food-antigen skin prick tests can provide a useful method for identifying an offending allergen. In their series, this occurred in 7% of individuals evaluated.[37]

The possibility that enhanced mast cell "releasability" due to the extracellular cytokine milieu bathing these cells might be present has also been investigated. The fact that a large number of patients with idiopathic anaphylaxis are atopic suggested that perhaps an increase in Th2 cytokines could lower the threshold dose for mast cell degranulation to exogenous stimulus. Reed et al[55] did find that patients with idiopathic anaphylaxis exhibited higher levels of Th2 cytokines (IL-4, IL-5, and IL-13) produced by lymphocyte stimulation when compared with nonatopic individuals and individuals with allergic rhinitis. In fact, even patients who were nonatopic but who had episodes of idiopathic anaphylaxis were found to have higher levels of interleukins associated with a Th2 response.

Because episodes are more common in females patients, investigators looked at whether female hormones could lower mast cell and basophil degranulation thresholds. Results of these studies have been inconclusive.[57] Two of 4 women were reported to have developed remission of anaphylaxis when treated with a luteinizing hormone-releasing hormone agonist, and the responders had experienced anaphylaxis within 30 to 60 minutes of infusion during provocation testing.[59] These patients should not be labeled as having idiopathic anaphylaxis because another explanation was identified. Grammer et al[61] found that patients with idiopathic anaphylaxis exhibited the presence of activated T cells. They found that, when comparing patients with acute idiopathic anaphylaxis with those in remission, those experiencing episodes had a higher percentage of $CD3^+HLA^-DR^+$ cells. They also noted that patients who experienced episodes while on prednisone as well as patients who were in remission had a significantly higher percentage of activated B cells ($CD19^+CD23^+$) than did normal volunteers, but it was unclear as to whether these findings were a result of events or were part of the underlying pathology.[61]

Investigators tested whether idiopathic anaphylaxis might be from increased target organ sensitivity and reported that some patients with idiopathic anaphylaxis had increased sensitivity to the injection of histamine.[62] In contrast, there was no evidence for cutaneous hypersensitivity (threshold reactive concentration for a reproducible 5-mm wheal and/or erythema from histamine, leukotriene D4, and platelet activating factor) in idiopathic anaphylaxis compared with patients with chronic idiopathic urticaria[89] and actually less reactivity than for patients with allergic rhinitis or asthma.[90] These data are consistent with receptor downregulation from mediator release. In addition, it remains to be established whether patients with idiopathic anaphylaxis have impaired inactivation of platelet activating factor by platelet activating factor acetyl hydrolase as has been described in severe or fatal anaphylaxis from peanuts[94] and in survivors of anaphylaxis, including 5 patients with idiopathic anaphylaxis.[95] Histamine releasing factors have been found in patients with idiopathic anaphylaxis.[63] Finally, autoantibodies to the IgE receptor also have been noted.[28] But it is unclear as to whether these antibodies are active in producing the degranulation of mast cells.

The number of mast cells/mm^2 in biopsy specimens of skin has been reported as follows: normal, 38 cells/mm^2; idiopathic anaphylaxis or unexplained flushing, 72 cells/mm^2; urticaria pigmentosa or indolent systemic mastocytosis, nonlesional skin, 168 cells/mm^2; urticaria pigmentosa, lesional skin, 597 cells/mm^2; and indolent systemic mastocytosis, lesional skin, 721 cells/mm^2.[91] So, although the number of mast cells in nonlesional skin is higher than found in normal skin, it is approximately 10% of that found in lesional skin from patients with indolent systemic mastocytosis.[9] Thus, an increased mast cell burden does not appear to play a role, at least in the majority of patients.

When considering theories of pathogenesis, it is important to note that empiric treatment with prednisone has proved effective in reducing the number and severity of episodes of idiopathic anaphylaxis, consistent with a steroid-responsive condition.[8,17,68,72,75] The positive findings were of patients classified as having frequent episodes, which means 6 or more per year or 2 episodes in 2 months.[72] The decision to administer prednisone was made because empiric treatment with H1- with or without

H2-antagonists or acute only treatment with oral steroids and H1 receptor antagonists could not be counted on to avert future episodes of anaphylaxis.[68,72] However, Khan and Yocum,[81] in a retrospective review of 37 patients with a diagnosis of idiopathic anaphylaxis, found that patients treated with only antihistamines and adrenergics underwent remission or improvement as frequently as those treated with chronic glucocorticoids. Thus, the expectation of pharmacologically induced or spontaneous remissions of idiopathic anaphylaxis contributes to the challenges in elucidating pathogenesis. None of the aforementioned studies have produced a conclusive link of cause and effect between their findings and anaphylactic events. In spite of these studies, there has been no satisfactory mechanism that could account for idiopathic anaphylactic episodes, their onset, frequency, and remission.

PHYSICAL EXAMINATION

At the time of acute episodes of idiopathic anaphylaxis, urticaria, angioedema, or both were present in all 335 patients in the Northwestern University series, whereas objective evidence of upper airway obstruction was noted in 63% of patients.[17] This obstruction could consist of clearly observed tongue enlargement, voice change with proven laryngeal edema, oropharyngeal edema, or stridor. Wheezing dyspnea was present in 39% of patients and hypotension or syncope in 23%. Some patients present with anaphylactic shock and cyanosis with or without cardiac arrhythmia.[9,18,43,68] When the episode resolved, these findings cleared. A careful search for urticaria pigmentosa lesions should be made because the presence of these lesions suggests the presence of mastocytosis instead of idiopathic anaphylaxis.

DIAGNOSIS OF IDIOPATHIC ANAPHYLAXIS IN THE CONTEXT OF ITS DIFFERENTIAL DIAGNOSIS

Before making a diagnosis of idiopathic anaphylaxis, one must clearly establish that the episode(s) in question was truly anaphylactic. This step can necessitate reviewing medical records for evidence of laryngeal or posterior pharyngeal edema (by laryngoscopic examination or radiographic examination), tongue enlargement, hypotension, angioedema, and urticaria. One mimic of idiopathic anaphylaxis is the somatoform event first described by Choy et al[39] and Patterson et al,[41,46,66] and later reported by others.[32] In the somatoform reaction, patients have episodes that mimic anaphylaxis, but the symptoms are grossly out of proportion to observed findings.[39] For example, a patient may develop acute localized or generalized urticaria or flushing, or both but report simultaneous acute severe, wheezing dyspnea, or loss of consciousness.[39] Although the acute episode is very real to the patient, an objective assessment of patients who do not have true anaphylaxis can identify vocal cord dysfunction, panic attack, hyperventilation without airways obstruction, normal blood pressure and pulse rate despite syncope or light-headedness, frightening stridulous sounds from contraction of neck muscles,[92] transient reduction of pulse oximetry averted by distraction and deeper respirations, and scratch-induced short-lived, linear erythematous lesions without wheals that clear in 10 minutes (perhaps labeled "erythema fugax"). In patients with undifferentiated somatoform idiopathic anaphylaxis, empiric treatment with prednisone can increase the number of episodes as opposed to the expected decrease in idiopathic anaphylaxis.[27,45] Because the episode meets criteria for a somatoform event, the patient is convinced that the episode is genuine.[39] There is another form of anaphylaxis that can appear initially as idiopathic, in which the episodes are self-induced[40] and are a variation of Munchausen syndrome. Munchausen anaphylaxis is true anaphylaxis, whereas undifferentiated somatoform idiopathic anaphylaxis is not.[39] In Munchausen anaphylaxis, the patient "consciously lies" about the self-induction of events, which are produced by the surreptitious ingestion of a known allergen (drug or food). In any case of idiopathic anaphylaxis, the physician or health care professional who cares for the patient should always keep these types of reactions in mind if a patient is not responding to treatment.

Also, one should consider in the differential diagnosis some other organic conditions that can mimic idiopathic anaphylactic events or the ingestion of a hidden allergen. These include histamine poisoning attributable to Scombroidosis, which is due to the ingestion of "spoiled" fish. These episodes can be related to eating fish of the scombroid variety (tuna, mackerel) as well as non-Scombroid fish (mahi-mahi, bluefish, salmon, sardines, herrings, amberjack).[96] Histidine is converted to histamine by histidine decarboxylase derived from bacteria in the tainted fish. Alternatively, an example of the ingestion of a hidden allergen occurs when eating mite-contaminated foods when there is no evidence for antiwheat IgE antibodies.[97] Other conditions, such as the carcinoid syndrome,[98] vasointestinal polypeptide secreting tumors,[99] and paradoxical pheochromocytomas, should be considered.[100] However, urticaria and angioedema are not characteristic of the acute episodes of these conditions.

TABLE II. Some tests and procedures to help establish or refute the etiology of anaphylactic events

Skin tests to foods or to drugs when indicated
a. Skin tests by using standard commercially available extracts
b. Skin tests by using fresh food
Serum-specific IgE to foods and drugs when indicated
Consider a diagnostic-therapeutic trial with prednisone
Oral challenge
Serum anti−alpha-gal IgE
Baseline and during anaphylaxis serum tryptase
Baseline and during anaphylaxis 24-h urinary histamine metabolites
Prostaglandin D_2 (urine or plasma or urinary metabolite 9 α, 11 β-prostaglandin F2)
Peripheral blood c-KIT mutation for codon D816V
Bone marrow examination

APPROACH TO DIAGNOSTIC TESTS

Once it was learned that patients with frequent episodes of anaphylaxis of unknown cause would experience a reduced incidence and severity of episodes when treated empirically with prednisone, hydroxyzine, and, if tolerated, oral albuterol, this combination of drugs has been used as a diagnostic and therapeutic regimen.[7,27,72] In particular, if the episodes of anaphylaxis continued despite the first 2 weeks of a minimum dose of prednisone 40 mg daily, in nearly all cases, idiopathic anaphylaxis can be excluded.[46] Some tests to establish or exclude a cause of anaphylaxis can be performed (Table II). These may include skin and *in vitro* tests for serum-specific IgE to foods and drugs, serum IgE to alpha-gal, baseline and acute phase serum tryptase, 24-hour urinary histamine metabolites, urinary prostaglandin D_2, oral

TABLE III. World Health Organization (WHO) criteria for systemic mastocytosis*,†

Major criterion
The presence of multifocal dense aggregates of >15 mast cells as detected with tryptase or other special stains in bone marrow or other extracutaneous organs
Minor criteria
1. Atypical morphology or spindle shapes in >25% of the mast cells in bone marrow sections, bone marrow aspirate, or other extracutaneous tissues
2. Mutational analysis of KIT, showing a codon 816 mutation (eg, Asp816Val) in bone marrow, blood, or extracutaneous organs
3. Bone marrow or other extracutaneous mast cells expressing the surface markers CD2, CD25, or both
4. Baseline serum tryptase levels >20 ng/mL

*The definitive WHO diagnosis of systemic mastocytosis requires the presence of 1 major and 1 minor criteria, or 3 minor criteria.
†Data from reference 82.

TABLE IV. Suggested criteria for the diagnosis of mast cell activating syndrome*

1. Symptoms typical of those produced by mast cell degranulation
2. A substantial transient increase in mast cell mediators (a serum tryptase increase of 20% plus 2 ng/mL within 4 h of an anaphylactic event)
3. A response to agents attenuating production of activities of these mediators or diminishing their effects on the target organ

*Data from references 80 and 105.

TABLE V. Drugs that place patients at risk for a more severe episode or complicate therapy

Potential agents include
1. β-adrenergic blocking agents
2. Angiotensin converting enzyme inhibitors
3. Angiotensin blockers
4. Monoamine oxidase inhibitors
5. Certain tricyclic antidepressants (eg, amitriptyline)

challenges, peripheral blood for the mutation of the gene D816V, and, in some cases, a bone marrow examination. On occasion, fresh food "prick-to-prick" testing is more sensitive than testing with commercial extracts and has been used to identify a food culprit undetected via testing with commercial extracts.[84] Additional discoveries have altered our approach to the use of the laboratory to establish a causative agent. These are the discovery of the role of the carbohydrate determinant, alpha-gal,[54,65] and the recognition of the importance of mastocytosis and mast cell activating disorders as causes of anaphylactic events.[80,82,85,86]

In an elegant series of experiments Platts-Mills and Commins identified a novel IgE antibody to a mammalian oligosaccharide, alpha-gal that has been associated with 2 distinct forms of anaphylaxis, an immediate onset of an event to cetuximab, and a delayed onset of anaphylaxis, which usually occurs 3 to 6 hours after the ingestion of mammalian food products (eg, beef, pork, lamb).[54,65] This oligosaccharide, alpha-gal, is a major blood group substance of nonprimate mammals and is a target of IgG antibodies that are present in the sera of all individuals who are immune competent. Sensitization occurs via the bite of ticks. The predominant cause in the United States is the bite of the Lone Star tick, *Amblyomma americanum*, but cases have been reported from other countries due to other species. It is interesting that this IgE antibody to alpha-gal cross reacts with cat and dog allergens but does not appear to pose a risk for asthma. Of importance is that IgE anti—alpha-gal is usually not detectable by skin testing with commercially available extracts but can be detected in some instances by performing prick-to-prick or intradermal testing by using fresh mammalian meat. There also is a commercially available test to detect serum-specific IgE anti—alpha gal. In some areas, a significant number of originally considered idiopathic anaphylactic events are due to this mechanism.[54] A diagnostic clue is that the tick bite results in up to 2 to 3 weeks of itching, erythema, or swelling.[54]

Alpha-gal is suspected as a culprit in any case without known cause, especially in events that occur 3 to 6 hours after eating, particularly those events that begin in the early morning hours because, for unknown reasons, episodes are delayed in onset and occur hours after ingestion. The discovery that IgE anti—alpha-gal can produce episodes in previously diagnosed idiopathic anaphylaxis makes the consideration of ordering IgE anti—alpha-gal important in any instance in which the cause of the event(s) is unclear and there is delayed (3-6 hours) onset postprandial anaphylaxis.

The realization that indolent systemic mastocytosis and mast cell activating disorders can be responsible for episodes erroneously thought of as idiopathic also has altered our approach to patients. The seminal article that established a relationship between mastocytosis and mast cell activating disorders and idiopathic anaphylaxis was published in *Blood* in 2007.[64] In this article, Akin et al[64] studied patients who had been referred to the National Institute of Allergy and Infectious Diseases with confirmed idiopathic anaphylaxis or probable mastocytosis. After bone marrow examination, it was demonstrated that there was a clonal disorder of mast cells. From a cohort of 72 consecutive patients, they reported 12 patients with recurrent anaphylaxis who did not have characteristic bone marrow biopsy findings characteristic of mastocytosis. That is, the biopsy specimens did not meet the criteria established by the World Health Organization cited as necessary to establish a diagnosis of this disorder (Table III). But some of the patients did demonstrate one or more minor criteria for mastocytosis, for example, being positive for the 816D>V (D816V) c-KIT mast cell activating mutation.[64] Two of the 12 patients had baseline serum tryptase concentrations higher than 20 ng/mL.[64] Since that publication, a number of other studies that confirmed this observation have been published. These investigations have prompted a proposed change in the nosology and classification of anaphylactic events.[80] The new proposed nosology was derived at an international conference convened to establish a consensus-based, evidence-supported diagnostic criteria for mast cell activating syndromes.

This proposed nosology suggests that mast cell activating conditions be classified into 3 distinct categories:

1. Mastocytosis and mast cell activating disorders.
2. IgE-mediated anaphylactic events.
3. Idiopathic anaphylactic episodes.

Mast cell activating disorders resemble mastocytosis and can cause anaphylaxis but lack sufficient bone marrow findings to make a diagnosis of mastocytosis according to the criteria

TABLE VI. Drugs used empirically to prevent or lessen the severity of episodes of idiopathic anaphylaxis

Name of medication	Dosage in adults	Dosage in children
H1 receptor antagonist		
Cetirizine (as example)	≥10 mg daily	Ages 6 mo to 5 y, 5 mg daily; ages 6-11 y, 5-10 mg daily
Sympathomimetic drugs		
Albuterol orally if tolerated	2-4 mg twice daily	Ages 6-12 y, 2 mg twice daily
Ketotifen (orally)*	2 mg three time daily	Ages ≥3 y, 1 mg twice daily
Prednisone	40-60 mg each morning daily for 1-2 wk, then on alternate mornings for 1 mo, then taper by 5-10 mg monthly if the patient is not experiencing anaphylaxis; attempt to taper and discontinue prednisone (see text)	1-2 mg/kg each morning daily for 1-2 wk, then convert to alternate mornings (similar as for adults)
Omalizumab	Optimal dosage unknown	Optimal dosage unknown

*Ketotifen is neither available nor approved by the US Food and Drug Administration as an oral product in the United States.

established by the World Health Organization (Table III).[82] Such patients have some of the bone marrow findings seen in mastocytosis and also can have a gain in function mutations in c-KIT. The diagnostic criteria for a diagnosis of a mast cell activating disorder[80] are seen in Table IV. The importance of the establishment that mastocytosis and mast cell activating disorders can be the cause of idiopathic anaphylaxis lies in the fact that mast cell activating disorders, on occasion, can be controlled with tyrosine-kinase inhibitors.[85,86]

Baseline, asymptomatic elevations in serum tryptase, plasma histamine, 24-hour urinary histamine metabolites, or prostaglandin D_2 levels suggest the presence of these conditions. The traditional cutoff value of 20 ng/mL, used to establish an elevated level of serum tryptase, may be too high. Mastocytosis and mast cell activating disorders can be present in patients with lower concentrations of serum tryptase. An at-risk population for indolent systemic mastocytosis includes patients who have had Hymenoptera anaphylaxis and are found to have baseline serum tryptase concentrations >11.7 ng/mL.[83] Because the most reliable way to make a diagnosis of mastocytosis or a mast cell activating disorder is to perform a bone marrow biopsy, one is faced with the decision as to whether or not to do a biopsy of patients in whom no cause for anaphylaxis has been determined. When to do so remains a cause of debate. Repeatedly elevated serum tryptase concentrations (baseline and during episodes) should raise the issue.

MANAGEMENT

All patients with idiopathic anaphylaxis should be advised to avoid taking drugs that might complicate treatment or worsen an event (Table V). Risk-benefit analysis and consultation with the physician who originally prescribed the drug are involved in the process of deciding whether or not it is in the patient's best interest to discontinue the particular drug in question. The drugs to be considered in this regard are β-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, monoamine oxidase inhibitors, and certain tricyclic antidepressants. β-Adrenergic blocking agents antagonize the β stimulatory effects of endogenously secreted and exogenously administered epinephrine. Even if the β-adrenergic blocker is a selective cardiovascular blocker, it would still be relatively contraindicated because a cardiovascular response (as well as a pulmonary response) to epinephrine is essential in the treatment of anaphylaxis (as opposed to the treatment of asthma).

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers block the compensatory response to hypotension that is induced by the activity of angiotensin-2. Angiotensin-converting enzyme inhibitors also have a second and perhaps more important effect. They prevent the catabolism of kinins, which are synthesized during an anaphylactic event. Monoamine oxidase inhibitors and certain tricyclic tranquilizers complicate the use of epinephrine because they can prevent its catabolism. Monoamine oxidase inhibitors do so by inhibiting its degradation by monoamine oxidase and some tricyclic antidepressants by preventing reuptake of norepinephrine at nerve endings. (By analogy, a patient who uses cocaine and who presents for what appears to be anaphylaxis and receives epinephrine could experience a hypertensive crisis.) All patients with idiopathic anaphylaxis should also carry identification jewelry (eg, MedicAlert Foundation; Turlock, Calif) or information on them about their diagnosis.

Drugs used to prevent or lessen the severity of episodes are seen in Table VI. In planning for treatment, it is useful to determine if the patient has had a single or an infrequent episode of idiopathic anaphylaxis or frequent episodes (2 in the past 2 months or 6 in the past 12 months).[3,7,17,72] If the patient seemingly has a new diagnosis of idiopathic anaphylaxis, then prednisone (typically 60 mg each morning for an adult for a week), H1, and, optionally, H2 blockers should be the initial therapy.[3,72] If the evidence of mast cell activation resolves, which means that urticaria has also cleared in a week, then prednisone can be discontinued. However, if a patient already is known to experience frequent attacks of idiopathic anaphylaxis, then, in the second week and thereafter, treatment consists of prednisone administered as alternate day therapy at 60 mg for adults.[3,72] If the patient is asymptomatic, then prednisone can be tapered every 2 to 4 weeks until it is determined that the patient has had no more episodes of anaphylaxis and prednisone is not required or more episodes occur. This empiric approach along with H1 antagonist and albuterol (if tolerated) has proven very effective in reducing the frequency and severity of future reactions.[7,8,15,17,68,72]

Some patients enter remission despite having experienced life-threatening anaphylaxis. For the patients who are prednisone dependent, ketotifen, which also is a mast cell stabilizer, has been shown to be a particularly effective agent in this regard.[71] Sympathomimetic drugs have also been used (these include oral albuterol as well as previously ephedrine).[72] One can speculate on the role of the usefulness of other agents to prevent and treat

anaphylactic episodes. One such presently available class of drugs is the leukotriene antagonist. There are very sparse data in the literature regarding the role of this class of drugs in the management of anaphylaxis, and the results are mixed.[101,102] At this time, although theoretically these drugs may be of benefit, there is no strong evidence to support their use.

The decision to start prednisone therapy and a discussion of its efficacy is contained in a 2012 review article[3] and initial reports.[7,17,68,72] For patients with infrequent episodes of idiopathic anaphylaxis, the regimen of (1) acute management with epinephrine, systemic corticosteroids, and H1 receptor antagonists, and then (2) hydroxyzine usually at 25 mg three times daily for 6 months was not associated with a reduction in the frequency of future episodes or emergency department visits.[72] In other words, patients who experienced 2 episodes per 6 months were found to have no reduction in episodes or emergency department visits over the next 6 months with empiric hydroxyzine treatment.[72] Finally, in preliminary reports, omalizumab[76-78] has proven to be a very helpful agent in the prevention of attacks. We repeat here that it is essential that patients be educated about the necessity of carrying self-injectable epinephrine at all times. Epinephrine is the drug of choice for the acute event, and it has been shown that strong educational efforts are helpful in encouraging adherence to the instructions to keep an autoinjector available.[26]

For reasons that are not clear, the vast majority of patients with idiopathic anaphylaxis gradually improve, including patients who have frequent episodes and require prednisone and H1 (and/or H2 antagonists or albuterol) for months or even 2 to 3 years. Episodes decline in frequency and remissions occur in many instances but not necessarily in the absence of empiric treatment.[79,81] This information may help provide some partial degree of reassurance to patients who live with fear of the next episode of idiopathic anaphylaxis.

Methylene blue is a novel potential treatment for refractory anaphylaxis based on the index case of a 43-year-old patient with idiopathic anaphylaxis who developed acute urticaria and very severe, epinephrine resistant, wheezing dyspnea with a blood pressure reading of 170/90.[103,104] Methylene blue 1% (typical adult dose 1-2 mg/kg in 100 mL of 5% dextrose administered over 20 minutes) is a competitive inhibitor of guanylate cyclase, which may block vasodilation caused by nitric oxide.[103] Methylene blue is a monoamine oxidase inhibitor and can produce arrhythmias, pulmonary hypertension, and hemolytic anemia.

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